FEBRUARY 1958 Volume 73 Number 2

# PUBLIC HEALTH REPORTS

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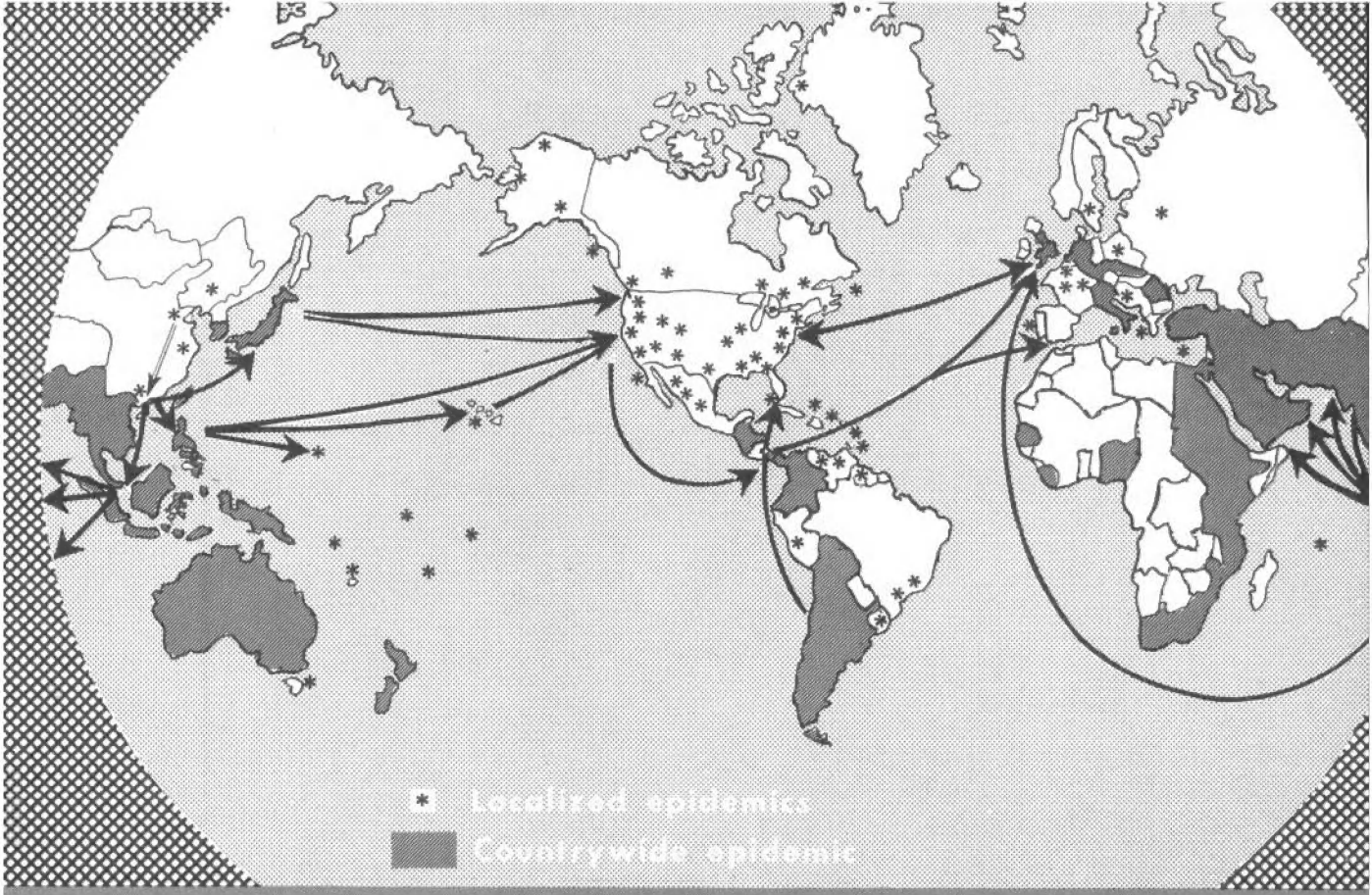
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service




# Early Routes of Asian Influenza Spread

The R. E. Dyer Lecture

# Influenza

## History, Epidemiology, and Speculation

RICHARD E. SHOPE, M.D.

WE ARE FACED at the moment with the most publicized influenza epidemic of all time, and there is great diversity of opinion concerning its eventual course and outcome. Some, who believe that the present outbreak is no different from those that have appeared periodically since the 1918–20 pandemic, contend that it will come and go without any serious effects and that the public is being unduly alarmed. Others feel that the present outbreak bears some of the earmarks of the epidemic illness that occurred in the spring preceding the great influenza pandemic of the autumn of 1918 and that, as such, may constitute but the first wave of a more serious type of influenza to follow. Those who consider that this speculation may have some probability believe that the time has arrived when we must attempt to determine whether our knowledge of influenza is advanced enough to permit a serious attempt at combating it or whether we are still in a phase where all we can do is conduct further studies of pandemic influenza. The latter group are of the opinion that an intensive program of widespread immunization with a vaccine containing the new influenza virus strain should be instituted with all possible promptness.

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The current epidemic of Asian influenza apparently started late in February of 1957 in Kweichow Province in southwest China. It spread to Yunnan Province in early March and was fairly well distributed through China by the end of that month. It spread to various

parts of the Orient during the following 3 months and reached the United States about the middle of May.

In this country, the disease spread slowly, involving initially military establishments that had received personnel returning from the Orient. It appeared in various groups of civilians that congregated from different parts of the United States during the summer, most notably in summer camps and in a summer church conference at Grinnell, Iowa. Ill individuals returning from these meetings set up foci of infection in their home communities, and by late July and early August the disease was widely seeded throughout the United States. During the early part of the outbreak, Asian influenza showed little tendency to spread except on very close contact and tended to remain sporadic. With the beginning of autumn, the disease diffused more widely and rapidly than it had at first (*1*).

The symptoms shown by individuals ill with influenza, consisting of fever, depression, anorexia, and variable respiratory signs, have been relatively mild and have lasted for 2 to 5 days. There have been to date relatively few deaths attributable to Asian influenza.

Asian influenza has as its primary etiological agent a type A influenza virus which appears, on serologic grounds, to be antigenically quite different from type A influenza viruses that have prevailed in previous outbreaks, swine, A, and A′ (*2*). It would appear from this that the world is being exposed to a virus with which it has had little or no previous experience and that, theoretically at least, we should be ripe for an extensive outbreak with the new agent.

The marked antigenic shift in the Asian virus, the deficiency of antibody against it in humans, and its relatively rapid spread and high attack rates in the Far East are features of the new virus that alarm many people. In addition, a number of the deaths that have occurred in our country have been in young adults, the age group that was hardest hit during the devastating 1918–20 outbreak. The suggestion from all this is that the current influenza virus has epidemiological and pathogenic potentials that must be taken seriously.

To lay groundwork for speculation about the possible course and outcome of the present outbreak of so-called Asian, or Far East, influenza, I should like to review briefly a little of what is known of past influenza pandemics. No one knows when pandemic influenza first appeared, although Hirsch (*3*) dates its initial recognition to the year 1173. Since then it has recurred at irregular intervals under various names: febris catarrhalis epidemica, tussis epidemica, and finally influenza. The most recent pandemic, that of 1918, was by far the most deadly ever experienced. During the 4 autumn months that it prevailed, it caused some 21 million deaths throughout the world. Nearly half a million of these occurred in the United States. Thus almost three times as many people died of pandemic influenza as lost their lives during the 4 years of World War I, which ended just as the 1918 pandemic was passing its peak.

I have selected three outbreaks of pandemic influenza to discuss, for comparative purposes, and to use historically in connection with my consideration of the present influenza outbreak. I have chosen one from olden days, before the speed of modern travel entered to confuse the epidemiological picture (1789), one from the beginning of the bacteriological era (1889), and one modern one (1918).

### Pandemic of 1789

The 1789 outbreak of influenza as it occurred in the United States was well described by Robert Johnson in his inaugural dissertation for the degree of doctor of medicine at the University of Pennsylvania in 1793. To orient you as to the time of this influenza outbreak, it came in the year that Washington was inaugurated President, that the first Congress met in New York, and that the French Revolution began. The first steamboat did not cross the Atlantic until 1819, and the first steam train did not run until 1830. Air travel, of course, was not even dreamed of. This outbreak occurred before modern means of rapid travel were available and when a man could go no faster than his horse could gallop. Despite this, according to Johnson, the influenza of 1789 spread like wildfire. It had the usual earmarks of later pandemics, being characterized by a prostrating illness of sudden onset and a febrile course of 4 to 5 days. Recovery was followed by several weeks of per-

**Pandemic and Interpandemic Influenza**

The term "pandemic" is ordinarily applied to a disease affecting or attacking all or a large portion of the population of a region: a disease extensively epidemic. Nothing in the usual definition of the term implies degree of severity. However, in current influenza parlance, the word "pandemic" has acquired a connotation of severity as well as extent of distribution. In this lecture pandemic designates a severe type of influenza such as that occurring in 1889 and during the autumn of 1918. The term "interpandemic influenza" denotes the milder type occurring between the pandemics at roughly 2-year intervals or oftener.

sistent coughing and prolonged debility in some instances. The attack rate was high, and the disease affected mainly persons in middle life.

The mortality rate was low, according to Johnson, and most patients recovered unless injudiciously treated. The suggestion was apparent in Johnson's paper that the treatment might frequently be more hazardous to life than the disease itself.

Now Johnson, in his definition of influenza, characterized it, among other things, as "a disease capable of being propagated by contagion." In spite of this conception, he could not completely rationalize the speed of its dissemination on the basis of transmission by contagion alone and visualized the importance of a "vicious quality of the air."

Johnson supported his contention about the spread of influenza by citing examples from the pandemic of 1782, in which he felt transmission by contact did not play the essential role. He stated, "Influenza appeared at London between the 12th and 18th, at Oxford in the third week, and at Edinburgh on the 20th day of May." He doubted that the disease could have been transferred to these three cities in such rapid succession "by things imbued with the contagion or by persons labouring under the complaint."

Later in his thesis he wrote, "On the 2d day of May 1782, the late Admiral Kempenfelt sailed from Spithead with a squadron under his command, of which the Goliath was one, whose crew was attacked with the influenza, on the 29th of that month: the rest were affected at different times: and so many of the men were rendered incapable of duty by this prevailing sickness, that the whole squadron was obliged to return into port about the second week in June, not having had communication with any shore, and having cruised solely between Brest and the Lizard."

Still another example was cited as follows, "About the 6th of May [in the same year 1782], Lord Howe sailed for the Dutch coast, with a large fleet under his command: all were in perfect health: towards the end of May the disorder first appeared in the Rippon, and in 2 days after in the Princess Amelia. Other ships of the same fleet were affected with it at different periods: Some indeed not until their return to Portsmouth about the second week in June. This fleet also had no communication with the shore until their return to the Downs, on their way back to Portsmouth, towards the 3d or 4th of June."

Johnson rationalized his views concerning the multiplicity of foci of origin of influenza during a pandemic by contending, "The morbific matter exciting the disease must have originated at some time and somewhere: and a cause like to that which gave rise to it in any one country, at any one point of time, might produce it in another country at the same time, under similar circumstances."

He continues, "I do not assert, nor do I wish to be understood to mean, that the influenza is not at all contagious: on the contrary, I am possessed of facts which prove in the most incontestable manner, that it may be, and often is, propagated from one person to another by means of contagion. But I mean, and the arguments which I have adduced, I trust, will warrant the conclusion, that the disease often does arise from some vicious quality of the air, or exhalation in it, as well as from a matter arising from the body of a man labouring under disease."

It is apparent that Johnson had certain difficulties in understanding and explaining the rapidity of spread of influenza. However, he did not have to make his views take into account the knowledge that influenza is an infectious

disease with a specific microbial cause, but instead could implicate various meteorologic abnormalities to explain incongruities that were beyond his comprehension.

I have gone into some detail in outlining opinions and observations concerning a premodern pandemic of influenza because I wanted to point out that influenza spread with unbelievable rapidity even before we had fast transportation to blame for its rapid and widespread diffusion and that, in the absence of such explanations to account for its dissemination, others, plausible at the time, were resorted to.

### Pandemic of 1889–90

The first pandemic of influenza in the bacteriological era was that of 1889–90. Finkler (*4*) has written, ". . . this influenza epidemic broke forth from the East, and overwhelmed the world in a pandemic such as had never before been seen. The high flood of the pandemic flowed over the whole globe in the space of a few months." It started supposedly in Bukhara in Turkestan in the month of May, though influenza was also prevalent in Greenland and in Hudson Bay territory at about the same time. Influenza did not become widespread in 1889 until October, when it prevailed over most of Siberia and European Russia. There it was supposedly first confused with dengue and later referred to as Siberian fever. By November it was prevalent over most of the rest of Europe, and in December was widespread in England and America. In the United States, the disease raged for about 2 months before subsiding, and there were periodic recrudescences during the next 4 years (*4*, *5*).

There seems to be general agreement that this pandemic had most of the characteristics of the greater one in 1918 except for its lower fatality. W. T. Vaughn (*6*), who studied the 1918 pandemic and thoroughly reviewed the literature dealing with that of 1889, wrote in his monograph on influenza, "The longer one studies the observations made in 1889–93, the more firmly convinced one becomes that the recent pandemic (1918) was identical with the former in practically all of its manifestations."

The main finding of value from the studies of the influenza pandemic of 1889–90 was the discovery by Pfeiffer of the so-called influenza bacillus (*7*). Pfeiffer believed that this organism was the cause of influenza because, according to him, it was present in all cases and not present in normal individuals unless they had recently recovered from influenza. Furthermore, it was associated with the lesions of the disease. Pfeiffer's views were widely accepted, and it is safe to say that the majority of medical people at the time believed that he had discovered the cause of influenza.

The 1889 pandemic may turn out to be of especial interest in connection with the current outbreak of influenza. Studies of the antibody content for the Far East strain of influenza virus in serum samples from persons of various ages have resulted in some very unusual and interesting findings: it has been noted that only samples from individuals 70 to 90 years old contain antibodies for this new virus (*8*, *9*). This finding may date the time of last occurrence of a virus of the serologic type of the present Asian strains, and the age distribution comes suggestively close to placing the time in the neighborhood of the 1889 pandemic. Thus there seems to be a possibility that we are at the moment experiencing a revisitation of the 1889 pandemic strain of influenza. This is, of course, speculative.

### Pandemic of 1918

During the spring of 1918 an influenza-like disease became prevalent in various parts of the world. This spring outbreak has been generally accepted as the first wave of the great 1918 pandemic. It is believed by epidemiologists to have been the immediate forerunner of the severe autumn outbreak which swept through the entire world with such deadly effect (*6*).

The first wave in 1918 received especial prominence in Spain, where it was said to have been sudden in its appearance and brief in its course, and to have subsided without leaving a trace. During April an illness similar to the Spanish epidemic occurred in American, British, and French troops in France, as well as in the civilian population. In England the first wave appeared in June and was composed for the

most part of mild cases (*10*). It affected simultaneously a large percentage of the population and showed a preference for individuals between 15 and 35 years of age. An influenza epidemic occurred also in Japan and China in the spring of 1918 (*11*). It was mild and was variously called "3-day fever" or "wrestler's fever," in addition to influenza. The spring wave of influenza was not highly diffusible; it reached only limited regions of Africa, largely missed South America, and affected Canada only slightly.

It is evident from accounts of the first wave that it was almost everywhere very mild so that although the morbidity was often high, sometimes amounting to 50 percent or more of the invaded population, the case fatality was exceedingly low (*10*). In many localities the general mortality rates were scarcely affected. In most countries the total number of persons contracting influenza seems to have been considerably smaller in the first wave than in the second.

The second wave, which proved to be extremely lethal, struck simultaneously in many parts of the world. It is generally stated to have appeared in Europe during the last week in August. In the United States it appeared first in Boston, supposedly from cases occurring on the receiving ship at Commonwealth Pier, during the last week of August also. During the next week it broke out among troops at Camp Devens in Massachusetts and sailors at the Great Lakes Naval Training Station in Illinois. Between the first and middle of September, hundreds of new foci appeared in various army camps, naval stations, and civilian communities. By the first week in October the pandemic was full blown throughout the entire world with the exception of a few islands and Australia. The height of the pandemic so far as this country is concerned was the fortnight between October 12 and 26 (*6*, *10*).

In the second wave, although there were many cases of the same mild type as in the first, perhaps as many as 80 percent of all attacks, a different manifestation of disease became prominent. This took two forms: (*a*) cases which started immediately with an acute pulmonary inflammation resulting in lung edema, violet cyanosis, and death within a few days, and (*b*) cases which developed on the fourth or fifth day of an ordinary influenza a definite bronchopneumonia which ran the usual course of primary bronchopneumonia of prepandemic times and was followed, accordingly, either by death or by a long convalescence (*12*).

Despite the fact that there was some divergency of opinion and considerable confusion concerning the epidemiological data, most epidemiologists believed that the 1918 autumn pandemic arose at 1 or 2 sites and from these spread throughout the world in a little over a month's time. It was commonly accepted, and there was evidence to support the opinion, that the pandemic in this country started in or near Boston (*6*, *10*). The cases responsible for the infection in Boston supposedly came from Europe, where the pandemic got under way very little, if any, earlier than it did in the Boston area. The infection was said to have been spread to other parts of the United States by the movement of patients among the civilian population or by the transfer of infected military personnel from one camp to another. The speed of spread was accounted for on the basis of the speed of available transportation. Certainly in a large number of instances, cited in the literature of the times, the onset of the disease in a community or a military establishment coincided very closely with the arrival of infected individuals.

However, certain discrepancies enter to spoil the perfection of the case-to-case transfer explanation for the spread of influenza during the second wave of the 1918 pandemic. These have to do with certain flukes in distribution, certain skips of large bodies of population. For example, Boston and Bombay had their epidemic peaks in the same week, while New York, only a few hours by train from Boston, did not have its peak until 3 weeks later (*10*). In like manner, Seattle, Los Angeles, and San Francisco had their epidemic peaks some 2 weeks earlier than Pittsburgh, which is just an overnight run from the infected eastern seaboard cities. In some respects, the epidemiologist had an easier time getting the pandemic disease transferred over long distances than in taking it to communities nearby. Thus, though it got to Chicago, presumably from Boston, fairly early and affected that city in September, it did

not reach Joliet, just 38 miles away, until October. Similarly, it took 3 weeks to cross the little State of Connecticut from New London County to Fairfield County (*10*).

In the light of these various epidemiological ambiguities one cannot help wondering whether perhaps more than one mechanism of dissemination may have been operating during the 1918 pandemic to account, on the one hand, for the lightning-like spread of disease over large distances and, on the other hand, for its slower diffusion over relatively small distances. The suggestion is apparent that extensive and widespread preseeding of virus in a masked or occult form, with its almost simultaneous provocation to infectivity by a stress common to wide geographic areas, might better account for the appearance of extremely rapid dissemination over great distances than does the view that case-to-case transfer was the responsible mechanism.

In swine influenza, a disease that I shall discuss a little later, the causative virus is preseeded in a masked, noninfective form by means of an intermediate host, the swine lungworm (*13*). Swine preseeded in this manner with occult virus remain normal to all outward appearances. However, all that is required to bring them down with influenza is the application of some stress of itself relatively innocuous. The stress, operative in nature for swine influenza, is meteorologic in character and is associated with the onset of cold, wet, inclement weather in the autumn (*14*). Swine that have been preseeded with masked influenza virus come down almost simultaneously in geographically widely separated areas when subjected to the same meteorologic stress, and the resultant widespread outbreak of influenza creates the illusion of being a disease that has diffused over an extensive area with unbelievable rapidity (*15*). Secondary cases of swine influenza follow at a more leisurely pace as a result of case-to-case contact with the primary, provoked infections.

I do not mean to imply, of course, that during the 1918 pandemic, the swine lungworm preseeded influenza virus in the human population. What I should like to suggest, though, is that influenza virus may be capable of existing in a masked form, similar to that found in the swine lungworm, in the human respiratory tract and that in such form it may be widely preseeded throughout a human population. It seems possible even that such preseeding may have been one of the functions of the milder, more slowly diffusing first wave of the 1918 influenza pandemic.

To return to further consideration of the 1918 pandemic, it may be said that, despite the apparent epidemiological discrepancies to which I have called attention, the opinion that direct and indirect transmission from man to man could account for the observed epidemiological picture of pandemic influenza was generally accepted. Whatever the correct explanation may be for the wide dissemination of the 1918 autumn pandemic, there is no doubt that the disease became very extensively distributed in short order. This second wave differed from the first in that it was more severe, more widespread, of greater dispersive power, and in some places at least, of a different age incidence.

The mortality rates recorded during the second wave varied widely among different groups and communities. The case fatality rate ranged from 3.1 percent in New London, Conn., to 0.8 percent in San Antonio, Tex. (*16*). Military personnel were especially hard hit, and Vaughn and Palmer (*17*) have stated that during the 4 autumn months of 1918, 1 of every 4 soldiers in the United States had influenza, 1 of every 24 developed pneumonia, and 1 of every 67 died.

### Efforts to Prove Contagiousness

With all of the observed clinical and epidemiological evidence pointing to the likelihood that the 1918 pandemic influenza was highly contagious and spread from sick to well easily and apparently at the very first available opportunity, one would have anticipated that proof of its contagiousness by transmission tests in human volunteers would have been extremely easy. However, such did not prove to be the case: in not a single controlled experiment was it possible to demonstrate the transmissibility of the disease.

The most carefully planned and conducted experiments were those carried out by the Navy and the Public Health Service. In the series

of experiments conducted in Boston during November and December 1918, 62 volunteers between 15 and 34 years of age were used (*18*). Thirty-nine of these had no history of having had influenza at any time, although apparently some degree of exposure had occurred. Filtered and unfiltered secretions from the upper respiratory tracts of patients with typical influenza were sprayed into the nose and throat and instilled into the eyes of some of the volunteers; direct swabbing from nasopharynx to nasopharynx was the method of exposure for others; and in one experiment freshly drawn citrated blood was injected subcutaneously. The results were summarized as follows: "In only one instance was any reaction observed in which a diagnosis of influenza could not be excluded, and here a mildly inflamed throat seemed the more probable cause of the fever and other symptoms. Nothing like influenza developed in the other volunteers."

In an attempt to imitate nature more closely, 10 volunteers were exposed to patients with acute influenza in hospital wards. Each volunteer was placed very near the patient, shook hands with him, chatted with him for 5 minutes, and then received the patient's breath full in his face five times while he inhaled. Finally the patient coughed five times directly in the subject's face. Each volunteer did this with each of 10 different patients, all of them acutely ill for not more than 3 days. All patients used had typical acute cases selected from a distinct focus or outbreak of disease. None of the volunteers developed the disease.

A second series of similar experiments was carried out in San Francisco during the same period also with completely negative results (*19*).

These two groups of experiments were considered to show that the requirements for the transmission of influenza from man to man, such as apparently exist commonly under natural conditions, are not readily imitated experimentally. Actually they constituted probably a very good demonstration of how solid an immunity was conferred by even a subclinical bout with the etiological agent of the 1918 influenza.

Much work was expended during the 1918 pandemic in an effort to determine the causative agent of the outbreak. Prior to the 1918 studies, *Hemophilus influenzae* had been generally regarded as the agent responsible for influenza. It seems quite natural, therefore, that much of the 1918 investigative work should have been concerned with a further study of the relationship of this bacterium to the disease. The results obtained were frequently confusing and contradictory, which is not surprising in view of the fastidious character of the organism and the technical difficulties associated with its isolation from the respiratory tract. It is difficult to give an accurate appraisal of the significance of the large amount of work done during the 1918 pandemic in trying to prove or disprove the etiological relationship of the Pfeiffer bacillus to influenza. About all that can be said is that the role of the organism was more controversial after the smoke of the 1918 pandemic studies had cleared than it had been before.

With the failure to gain clear-cut evidence that *H. influenzae* was the cause of the 1918 pandemic, the view was rather widely held and was frequently expressed that a virus was probably the etiological basis for the disease. This actually constituted no more than an ungrounded opinion, for consideration of the data on the subject published from 1918 investigations reveals that no one adduced good evidence to incriminate a virus as the causative agent. The upshot of a terrific amount of effort during the 1918 influenza pandemic to learn the cause of the disease was to weaken the view that Pfeiffer's bacillus was the etiological agent and to substitute no other in its place.

I have just indicated that no one succeeded in determining the causative agent responsible for the 1918 pandemic influenza. This is not strictly true and what I should have said is that no investigator working in a laboratory did it. Actually Mother Nature stepped in and took care of the situation for us, as I shall now point out.

### Swine Influenza

At the height of the second wave of the 1918 pandemic, a new disease appeared among swine in the Middle West. This new disease was not a sporadic and localized outbreak; actually millions of swine became ill and thousands died

during the first few months of its occurrence. The epizootic persisted in various localities until January 1919 and reappeared in the autumn and winter of that year as extensive and severe as in 1918. It has recurred each year since then, but it varies annually in its severity and extent.

Dr. J. S. Koen, an inspector in the Division of Hog Cholera Control of the U. S. Bureau of Animal Industry, was the first to recognize that the disease was different from any previously encountered (*20*). He was so much impressed by the coincidental prevalence of human influenza and by the resemblance of the signs and symptoms seen in man to those occurring in hogs that he become convinced that the two were actually the same. He therefore gave the name of "flu" to this new disease of hogs. The opinion of Koen that "flu" represented an entirely new swine epizootic disease and that swine might have been infected in the first instance from man was shared by some veterinarians and many farmers in the Middle West (*21*).

Everything was not rosy, however, with Koen's contention that a direct causal relationship might exist between the swine and the human diseases. The basis for the objections was largely economic since it was feared that, if it became widely known that swine could acquire human influenza, the pork-consuming public might become alarmed and the pork market would be adversely affected. Koen, however, was a fiery little man and, though frequently forced to defend his convictions verbally, stuck to them steadfastly. A year after his choice of what seemed a most unpopular name and diagnosis, he defended himself as follows (*22*):

"I have no apologies to offer for my diagnosis of 'flu.' Last fall and winter we were confronted with a new condition, if not a new disease. I believe I have as much to support this diagnosis in pigs as the physicians have to support a similar diagnosis in man. The similarity of the epidemic among people and the epizootic among pigs was so close, the reports so frequent, that an outbreak in the family would be followed immediately by an outbreak among the hogs, and vice versa, as to present a most striking coincidence, if not suggesting a close relation between the two conditions. It looked like 'flu,' it presented the identical symptoms of 'flu,' and until proved it was not 'flu' I shall stand by that diagnosis."

The late Dr. Paul A. Lewis and I began our studies of swine influenza during the autumn of 1928, and we were elated and pleased when we isolated from our very first cases of the disease an organism that was, so far as we could tell, like the non-indol-producing strains of Pfeiffer's bacillus (*23*). We named this organism *Hemophilus influenzae suis*. We isolated the same organism from field outbreaks of swine influenza again in 1929 and in 1930. It was the only organism we found with any regularity, and somtimes it was the only one present in the respiratory tracts of sick swine. Unfortunately, so far as assigning it etiological importance was concerned, *H. influenzae suis* administered in pure culture to susceptible swine produced no illness. We were thus faced with the dilemma of having found an organism that seemed always to be present in cases of the disease, that was demonstrable at the sites of the influenza lesions in the respiratory tract, but that failed to induce disease when administered to normal swine.

It was subsequently found that a filtrable virus, differing from any hitherto known, was important in the causation of swine influenza (*24*). This virus, however, was not the sole cause of swine influenza: when the virus was administered alone to susceptible swine it produced a disease that was clinically much milder than the true swine influenza as seen under natural conditions.

It was finally determined that swine influenza was a disease of complex etiology and that both the bacterium *H. influenzae suis* and the new filtrable virus were etiologically essential (*24*). We thus had in swine influenza a disease caused by the concerted activity of two agents, one of which, the bacterium, was strikingly like Pfeiffer's bacillus, long suspected by many of playing a causative role in human influenza. The other agent etiologically essential was completely new and did not, so far as anyone knew at the time of its discovery, have a counterpart in human disease. As it later developed, however, when Smith, Andrewes, and Laidlaw (*25*) demonstrated a virus as the cause of an in-

fluenza outbreak in 1933 and when this new virus was compared with the one from swine influenza, the two were found to be strikingly alike. They affected the same species of animals; they gave a high degree of cross protection against each other; and they could only certainly be differentiated from one another on the basis of certain serologic tests (*26–29*).

Thus in 1933 we had for consideration the intriguing situation of an animal disease of complex etiology, resembling influenza, in which one of the essential agents resembled the bacterium found extensively present in the second wave of the 1918 influenza pandemic and in which the other essential agent resembled the virus responsible for the then current interpandemic influenza. It seemed that, despite the failure of human investigators of the 1918 influenza pandemic to discover the cause of the outbreak, Mother Nature, using swine as her experimental animals, had done so. Furthermore, she had apparently segregated not one human agent but two from the disease of the severe second wave.

The late Sir Patrick Laidlaw (*30*) and I (*31*) summarized the indirect historical and experimental evidence bearing on the relationship of swine influenza to pandemic human influenza and pointed out that it strongly indicated the likelihood that swine had indeed acquired their infection naturally from man in 1918 and that the swine influenza virus was, therefore, the surviving prototype of the 1918 pandemic virus. Two further bits of experimental evidence have subsequently been developed in support of the hypothesis. In serologic tests conducted against swine influenza virus with serum samples from humans of various ages in 1935 and 1936, the results were such as to indicate strongly that an agent of the swine influenza virus type had been widely prevalent in man in the period from 1918 to 1920 and had not been present since then (*32*, *33*). In like manner, serologic tests conducted in 1952 (*34*) with swine influenza virus and the serums of humans of various ages again pinpointed the time of prevalence of an agent of the swine influenza virus type to the 1918–20 period. These two sets of studies, one carried out 17 years and the other 34 years after the 1918 pandemic, both orienting the time of prevalence of a virus of the swine influenza type to the period 1918–20, would seem rather effectively to support the view that swine influenza represents the surviving prototype of the agent that prevailed in man during the second wave of the 1918 influenza pandemic.

In brief, it seems to me that, from the swine influenza findings, one is warranted in speculating that the second wave of the 1918 influenza pandemic had as one of its etiological components a virus that was serologically closely related or identical to the swine influenza virus. It was, therefore, a type A virus not too much unlike the type A viruses with which we have had experience in the influenza outbreaks since 1933.

I am further going to assume for speculative purposes that the etiology of swine influenza as we know it today represents accurately the etiology of the second wave of the 1918 pandemic and that back in the autumn of 1918, when swine acquired their disease from man, the pigs effectively segregated the important etiological components of the human disease, namely, Pfeiffer's *H. influenzae* and a type A influenza virus. I hope that you will not consider this last assumption too illogical because to me it appears completely reasonable that, if an experimental host can select the etiologically essential virus, it might equally well be expected to select, from the mixture of micro-organisms that prevailed during the second wave of the 1918 outbreak, the etiologically important bacterium.

### Evidence of Immunity

A question of very great interest to us right now, when we are in the midst of an outbreak of mild influenza which may turn out to be the first wave of a more severe outbreak, is what constituted the difference between the mild first wave and the severe second wave of the 1918 pandemic. I have speculated, on the basis of the swine influenza work just discussed, that the second wave of the 1918 pandemic was caused by a type A influenza virus, of which the swine influenza virus is the surviving prototype, acting in concert with *H. influenzae*. What then caused the first wave, and why was the first wave so much milder than the second one? Are there any data

from the investigative work conducted during the 1918 outbreak that might shed light on the relationship of the one wave to the other? I believe that there are and that they concern the question of immunity conferred by an attack of influenza during the first wave against infection during the second.

Because this question of the presence or absence of an immunological relationship between the first and second waves of the 1918 influenza has an important bearing on my speculations, I should like to cite several examples dealing with this point.

The Annual Report of the Surgeon General of the Navy for the year 1919 says in part, " . . . many men of the Navy who had influenza in the spring or summer of 1918, while in European waters, escaped during the later epidemics (winter 1918–19) both in Europe and the United States. The British Grand Fleet experienced the same thing: with few exceptions those men who contracted influenza in May and June were not attacked during the more fatal epidemics in October, November, and December. The conclusion is that mild attacks earlier in the year, as a rule, conferred immunity against the more fatal type of the disease which prevailed subsequently." With regard to the experience in the British Navy, Dudley (*35*) has pointed out that the crews of only certain ships were affected by the first wave, the crews of others escaping the infection. During the second wave the attack rate on the ships that had had the earlier infection was about 25 percent, while on those ships that escaped the first wave the attack rate was about 50 percent.

In most Army groups the outfits were moved about too much and transferred too frequently to furnish reliable records as to an immunological relationship between the two influenza waves in 1918. There are, however, large numbers of isolated records involving relatively small numbers of individuals. For instance, Gibbon (*36*) writes that of 400 patients with influenza hospitalized from among the 2,000 troops under his care, none admitted in June, July, or August was readmitted in October, November, or December, and none admitted in either of those periods was readmitted in February 1919. Dopter (*37*) reports recurrent epidemics in a French Army division of which he was surgeon in 1918. During the spring wave, toward the end of April, only the infantry regiment of the division was attacked, the artillery regiment escaping infection. In the fall a group of heavy artillery was attached to the division, bringing influenza with it. The disease spread, but only those not ill during the first wave were very seriously ill in the second.

V. C. Vaughn (*38*) cites the experiences of the 2d Infantry Regiment which underwent influenza in June of 1918 in Hawaii before being transferred to Camp Dodge about August 1. When the severe second wave hit Camp Dodge in September and October, the 2d Regiment was only slightly affected, although the attack rate for the camp as a whole was about 33 percent and the case fatality 6.8 percent.

Probably the most impressive example of immunity among troops is that related by V. C. Vaughn (*39*) for a division stationed at Camp Shelby. The division, numbering about 26,000, underwent a mild influenza epidemic of about 2,000 cases in April 1918. Vaughn comments as follows on the subsequent history of the division: "This was the only division that remained in this country without change of station from April until the fall of 1918. During the summer this camp received 20,000 recruits. In October 1918 the virulent form of influenza struck this camp. It confined itself almost exclusively to the recruits of the summer and scarcely touched the men who had lived through the epidemic of April. Not only the 2,000 who had had the disease in April, but the 24,000 who apparently were not affected escaped the fall epidemic. It appears from this that the mild influenza of April gave a marked degree of immunity against the virulent form in October."

Certain information about the civilian population also indicated an immunological relationship between the first and second waves of influenza. Malone and McKendrick (*40*) observed in Calcutta that three institutional populations who experienced infection during the July wave passed through two later waves, in December 1918 and February 1919, without contracting the disease a second time. They believed that their evidence indicated an im-

munity lasting for at least 9 months. The Inspector General of Health in Spain (cited by W. T. Vaughn, reference 6) reported that those cities that had the disease in May 1918 suffered lightly in the autumn, while cities that had been spared in the first invasion suffered most in the second. V. C. Vaughn (*39*) has pointed out that among the large cities in the United States having a low death rate during the autumn wave of influenza were a number that had reported an unusually high incidence of influenza and pneumonia in the spring. Jordan (*10*) has called attention to the fact that the attack rates in English towns during the autumn wave were only about half those prevailing in towns in the United States and comments on the temptation to account for the differences on the basis of the more sharply defined and extensive first wave which prevailed in England having conferred a more extensive immunity. W. T. Vaughn (*6*) in studies deriving from his house-to-house canvasses in Boston found only four instances of more than one attack of influenza among 1,971 cases occurring in his series between March 1918 and August 1919.

There are, of course, some examples in the literature which fail to show a clear-cut immunological relationship between the two waves. My reason for calling detailed attention to the examples indicating a relationship and neglecting those that do not is this: When one is seeking to show a positive relationship between two conditions of unknown etiology, a positive correlation is, because of diagnostic uncertainties, of much more value in indicating the true relationship than is a negative one.

It is apparent, I believe, from the examples I have just cited that, by and large, an attack of influenza during the mild first wave protected an individual against infection during the more severe second wave. Such a relationship strongly suggests that the etiological agents responsible for the two waves were either identical or so closely related immunologically as to cross-protect one against the other. Since what presumptive evidence we have indicates that a type A influenza virus of the swine influenza prototype was involved in the second wave during 1918, the assumption seems warranted from this immunological data that the same or a very closely related type A virus was also involved in the first wave. Why then, since similar influenza viruses were apparently of etiological importance in each of the waves, were the two waves clinically so different?

### Role of H. Influenzae

A possible answer to this question, I believe, is supplied by the bacteriological studies of those investigators who sought to find the Pfeiffer bacillus during both waves of the 1918 pandemic. As I have pointed out, from the time of Pfeiffer's announcement of its discovery in 1892 until 1918, *H. influenzae* was generally regarded as the agent responsible for epidemic influenza. Because of this belief, much of the work done during the 1918 pandemic was concerned with a further study of the relationship of this bacterium to the disease.

In the light of this large effort to find *H. influenzae*, the marked difference encountered in the incidence in which it was demonstrated during the first and second waves by individual investigators who studied both waves was striking and suggestive. The findings of almost all were in agreement that the Pfeiffer bacillus was either absent or of low incidence in cases of the first wave and abundantly present during the second wave. Sobernheim and Novakovic (*41*), for instance, found Pfeiffer's bacillus to be practically absent from the early cases, whereas in the second wave they found it in pure culture in a large majority of the cases investigated (18 out of 23). Fildes, Baker, and Thompson (*42*) failed to find influenza bacilli in cases during July and August but found them during the autumn wave in the sputum of 12 of 15 uncomplicated cases and in practically all their postmortem material. Similarly, McIntosh (*43*) failed in the summer but found Pfeiffer's bacillus in the autumn in 8 of 12 examinations of the nasopharynx in uncomplicated cases, and in the sputum of 21 of 25 cases with bronchopneumonia. The experience of others both in Europe and in the United States was similar (*44–47*).

In this country, for example, Opie, Blake, Small, and Rivers (*47*) found that the incidence of Pfeiffer's bacillus in normal individuals from isolated communities, or in groups free from respiratory disease prior to the occur-

rence of the 1918 autumn epidemic, was relatively low (10 to 20 percent), but that before the fall epidemic, in groups in which bronchitis and pneumonia were fairly prevalent, the incidence was higher (25 to 50 percent). During the epidemic the incidence rose to 95 percent.

I believe it can be safely said that, so far as the bacteriology of the first wave of the 1918 influenza epidemic can be used as a criterion, Pfeiffer's bacillus was not demonstrated with enough frequency to support its claim as a causative agent. Its presence probably about coincided with its distribution in healthy persons at the time that the first wave appeared. During the second wave, however, the organism appears to have been found with great regularity.

In summary then, it appears that the Pfeiffer bacillus was absent or of low incidence in cases of the first wave and was almost uniformly present in cases of the second wave. How then could these differences in the bacterial flora during the two waves have influenced the severity of a disease caused by a type A influenza virus? Here I must again revert to consideration of swine influenza for a possible answer to this question.

As I have indicated earlier, infection of swine with the swine influenza virus alone results in an extremely mild respiratory disease of 2 or 3 days' duration from which the animals uniformly recover. However, swine infected with the swine influenza virus in combination with *H. influenzae suis* undergo a severe prostrating, febrile illness of 4 or 5 days' duration, frequently accompanied by pneumonia, from which death results in about 3 percent of all cases. In swine, then, the disease caused by the swine influenza virus alone resembles, in its mildness and other clinical characteristics, that seen in man during the first wave of the 1918 influenza, while the disease caused by a concomitant infection with the virus and *H. influenzae suis* resembles that seen during the second wave of the 1918 influenza. Furthermore, swine recovered from the mild ailment caused by infection with the virus alone are solidly immune to the more serious disease caused by infection with the virus plus *H. influenzae suis* (*48*).

It seems apparent, if the analogy between swine influenza and the 1918 influenza pandemic is an acceptable one, that the mild first wave of the 1918 pandemic can then be interpreted as one in which only a type A virus of the swine influenza prototype was involved. The second wave, on the other hand, was one in which the infection was a complex one, involving the same or an immunologically closely related type A virus and *H. influenzae*.

### Applications to Present Outbreak

Let us now return to the current Asian influenza outbreak. If this outbreak is eventually to reach serious proportions, we appear at the moment to be in what in 1918 was the first wave. The cases ordinarily are not severe, and the mortality rate is relatively low. So far as I am aware, the Pfeiffer bacillus is not being isolated with any regularity from cases, and certainly it has not been reported to have been present in cases that have come to autopsy.

The current influenza may be considered on clinical grounds to be similar to a number of the outbreaks of interpandemic influenza that we have experienced since 1932 or to the first wave of the 1918 pandemic. We have no way of knowing at the moment whether it will be followed by a second wave of greater pathogenicity, as was the first wave in 1918. The fact that the human population is, in this outbreak, experiencing infection with a virus with which it has had no previous experience, to judge from the absence of specific antibodies, suggests that we may be ripe for a continuation of the present epidemic into a severe and killing second wave, but I do not think that anyone is, at the moment, in a position to predict accurately on this point.

Now, in the light of the speculations in which I have indulged, I should like to outline briefly my views as to how the present outbreak should be handled from a practical standpoint.

I believe it would be very foolish not to take full advantage of what means we have to protect ourselves. By this I mean that vaccination against the current epidemic strain seems to me to be strongly indicated. I think it is especially urgent that those who have apparently missed clinical infection during the early part of the present outbreak be immunized, since

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